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Urinary Catecholamine Excretion and Severity of PTSD Symptoms in Vietnam Combat Veterans

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In the present study, we replicated and extended our previous findings of increased 24-hour urinary catecholamine excretion in posttraumatic stress disorder (PTSD). Dopamine, norepinephrine, and epinephrine concentrations were measured in 22 male patients with PTSD (14 inpatients and eight outpatients) and in 16 nonpsychiatric normal males. The PTSD inpatients showed significantly higher excretion of all three catecholamines compared with both outpatients with PTSD and normal controls. Dopamine and norepinephrine, but not epinephrine, levels were significantly correlated with severity of PTSD symptoms in the PTSD group as a whole. In particular, these catecholamines seemed related to intrusive symptoms. None of the catecholamines were correlated with severity of depression. The findings support the hypothesis of an enhanced sympathetic nervous system activation in PTSD, and suggest that increased sympathetic arousal may be closely linked to severity of certain PTSD symptom clusters.

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Ongoing studies in our laboratory have utilized psychoneuroendocrine measures to explore catecholamine regulation in posttraumatic stress disorder (PTSD; for review, see Mason et al., 1990; Yehuda et al., 1990a). In a preliminary study, we reported that hospitalized combat veterans with PTSD have sustained elevations of 24-hour urinary norepinephrine and epinephrine compared with patients in other diagnostic groups (Kosten et al., 1987). Consistent with this, we observed a decreased number of alpha-2-adrenergic receptors in PTSD patients compared with normal subjects (Perry et al., 1987, 1990; Yehuda et al., 1990b).

Laboratories using other biological approaches have also provided evidence for increased catecholamine activity in PTSD. For example, psychophysiological studies have shown that combat PTSD patients exhibit exaggerated sympathetic nervous system responses to reminders of war trauma (for review, see Krystal et al., 1989). Challenge studies have shown that noradrenergic activating agents, such as lactate (Rainey et al., 1984) and yohimbine (Southwick et al., 1990a) elicit sympathetic and PTSD symptoms in war veterans. There is also evidence that some PTSD symptoms can be alleviated by medications that can affect CNS noradrenergic activity (Davidson et al., 1991; Frank et al., 1988).

While the findings of increased catecholamine system activity seem fairly consistent across published studies, the extent to which catecholamine alterations observed in PTSD are specifically related to severity of PTSD symptoms is currently unclear. Most biological studies in PTSD have tended to focus primarily on inpatients who are quite symptomatic when they are studied, and, accordingly, represent a relatively homogenous group with respect to severity of symptoms. In the present study, we attempted to address the relationship between catecholamine and severity of PTSD symptoms by measuring 24-hour urinary catecholamine excretion and severity of psychiatric symptoms in inpatient and outpatient combat veterans with PTSD across a wide range of PTSD symptom severity.

Methods

Twenty-two nonmedicated, male Vietnam combat veterans with a primary diagnosis of PTSD and 16 nonpsychiatric men gave written informed consent to participate in the study. Sixteen of the subjects were inpatients at the Psychiatry Service of the West Haven Veterans Hospital and eight were outpatients recruited from the New Haven Outreach Center. Patients and normals were age comparable (mean ± SD for age,

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40.37 ± 2.06; PTSD, 39.78 ± 7.9, normals $t = .30$; $df = 32$; NS).

Combat exposure was rated on a scale of 1 to 14 using the Combat Exposure Scale (U.S. Government Printing Office, 1981), with scores ranging from 7 to 14 (moderate to heavy exposure) in our sample. Posttraumatic stress disorder was diagnosed using the Structured Clinical Interview for the DSM-III-R (Spitzer et al., 1987). Other diagnoses were made according to Research Diagnostic Criteria (RDC; Spitzer et al., 1978) using the Schedule for Affective Disorder and Schizophrenia (Endicott and Spitzer, 1978). Subjects with major medical illness, organic brain syndromes, schizophrenia, bipolar disorder, and current substance abuse were excluded from the study. Patients with a primary diagnosis of major depressive disorder were also excluded from the study, although three of the inpatients and two of the outpatients met RDC criteria for secondary depression. None of the patients met diagnostic criteria for generalized anxiety disorder; however, four of the inpatients met criteria for panic disorder. Patients were not receiving any medications, including hypertensives or other drugs that might interfere with catecholamine metabolism. Routine urine toxicology screening further confirmed that subjects were free of psychotropic drugs or illicit substances at the time of sample collection.

Urine samples were collected and stored frozen on dry ice during the collection day to preserve catecholamines. Sampling in both patient and comparison groups was avoided during the week of admission to the hospital (inpatients), on days of unusual physical activity or stress, and also during periods when unusual procedures, including endocrine challenge tests (inpatients), were being performed. Completeness of collections was monitored by nursing staff for the inpatients, and by determinations of urinary creatinine excretion for all patients and comparison subjects. Mean creatinine excretions ranged from .8 to 1.9 g/day, which is within the normal range (Mason et al., 1986). Following rapid standardized thawing, a 2.5-ml aliquot of urine was adjusted to pH 2.0 with concentrated HCl and, following the addition of 20 µl EDTA/reduced glutathione solution/ml urine, refrozen at −70°C until analyzed for catecholamines by high-performance liquid chromatography (HPLC). Urinary norepinephrine (NE), epinephrine (EPI), and dopamine (DA) excretion rates were measured by HPLC using a Waters system with a model 712 automatic sample processor, a Bio-Rad cation exchange silica column with a microguard system, and an ESA Coulochem model 5100A electrochemical detector. *N*-Methyldopamine was employed as the internal standard. For sample preparation, microcation columns filled with weakly acidic cation exchange resin were used (Bio-Rad, Hercules, CA). The interassay coefficients of variation were 8% for norepinephrine, 4% for epinephrine, and 3% for dopamine. Analytical recovery was 103% for NE, 98% for EPI, and 95% for DA.

The PTSD symptoms were assessed using the Impact of Events Scale (IES; Horowitz et al., 1979), which contains two subscales for the determination of intrusive versus avoidance symptoms, and the Figley PTSD Interview (Figley and Stretch, 1980). Depressive symptoms were measured with the Hamilton Depression Rating Scale (Hamilton, 1960). Symptom ratings were made at the termination of the 24-hour urine collection.

Differences between the three groups in catecholamine levels were determined using one-way analysis of variance (two-tailed), followed by post hoc comparisons using the Fisher least significant difference test. Differences in clinical symptomatology between inpatients and outpatients were determined using Student's *t*-test. Correlational analyses were performed on biological and clinical measures from PTSD patients using Pearson's coefficient *r*. Bonferroni corrections were applied to correct for multiple comparisons. Thus, for determining significance of correlations between catecholamine and clinical symptoms, an alpha level of $p < .0125$ was used; in determining significant intercorrelations among catecholamine measures, an alpha level of $p < .008$ was used.

Results

Figure 1 illustrates the mean 24-hour urinary excretion of DA, NE, and EPI in the PTSD and normal comparison groups. Analysis of variance revealed a significant main effect of group for DA ($F = 8.07$, $df = 2,35$; $p < .001$), NE ($F = 14.3$; $df = 2,35$; $p < .0001$), and EPI ($F = 5,39$; $df = 2,35$; $p < .009$) excretion. Post hoc testing confirmed that inpatients with PTSD were significantly higher than the outpatient PTSD and normal control groups on all catecholamine measures. Compared to normal controls, PTSD inpatients showed a 44% greater concentration of urinary DA, an 85% greater concentration of urinary NE, and a 46% greater concentration of urinary EPI. Inpatients with PTSD were also significantly higher than outpatients on all catecholamine measures. Inpatients showed a 25% higher urinary DA excretion, a 35% higher urinary NE excretion, and an 85% higher urinary EPI excretion compared with outpatients. Outpatients with PTSD were not significantly higher than normals on any of these measures.

Table 1 summarizes the clinical symptom data for the inpatient and outpatient PTSD groups. There was a wide range of both PTSD and depressive symptoms in the patient groups. Inpatients were significantly more symptomatic with regard to PTSD symptoms, as measured by the Impact of Events Scale ($t = 2.6$; $df = 18$; $p < .0125$). This was primarily due to the greater intru-

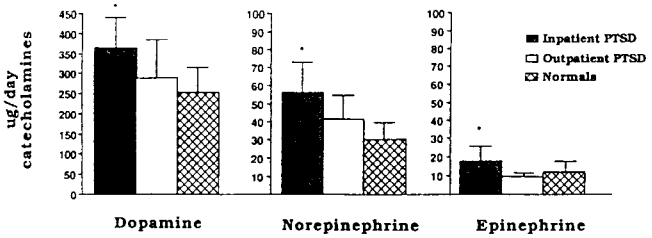

FIG. 1. Twenty-four hour urinary catecholamine excretion in PTSD inpatients, outpatients, and normal subjects. Asterisk indicates significantly different from normals and outpatients ($p < .05$)

TABLE 1
PTSD and Depressive Symptoms in the PTSD Groups[a]

Rating Scale	Range of Scores	Inpatients	Outpatients
Figley PTSD	4–48	30.9 ± 10.4	22.4 ± 10.7
IES total	7–61	40.4 ± 13.1[b]	22.1 ± 17.7
Subscales			
Intrusive	3–33	22.8 ± 8.0[c]	11.6 ± 8.7
Avoidance	1–38	18.1 ± 7.4	10.5 ± 12.1
HDRS	7–44	21.1 ± 11.8	18.0 ± 8.0

[a]Results are expressed as mean ± SD.
[b]$t = 2.6$; $df = 18$; $p = < .0125$.
[c]$t = 2.9$; $df = 18$; $p = < .008$.

sive ($t = 2.9$; $df = 18$; $p < .008$), but not avoidant ($t = 1.8$; $df = 18$; $p < .090$), symptoms. Inpatients also showed a nonsignificant 30% greater mean Figley score compared with outpatients ($t = 1.55$; $df = 14$; NS). Depressive symptoms were comparable in both groups ($t = .68$; $df = 18$; NS).

Correlational analysis revealed significant relationships between 24-hour urinary DA and NE excretion and PTSD symptoms. Both DA and NE were significantly correlated with total IES scores (Table 2), with both catecholamines being particularly related to the intrusive symptom cluster. Levels of both catecholamines also showed a trend for a relationship with avoidance symptoms. There was also a strong trend for a relationship between the urinary excretion of DA and scores on the Figley scale, which assesses intrusive, avoidant, and hyperarousal symptoms. Urinary EPI concentrations were not correlated with PTSD symptoms. None of the three catecholamines was correlated with Hamilton Depression Rating Scale scores.

Catecholamine levels were also not significantly intercorrelated in either the PTSD or normal groups. However, there was a strong trend for a relationship between DA and NE excretion in the PTSD group ($r = .65$; $df = 36$; $p < .001$).

Discussion

The results of the present study replicate our previous finding of increased 24-hour urinary catecholamine excretion in combat veterans with PTSD compared

TABLE 2
Correlations among Catecholamines and PTSD and Depressive Symptoms

	Figley[a]	Impact of Events Scale Total	Intrusive	Avoidant	HDRS
Dopamine	59**	63*	68*	.49***	.12
Norepinephrine	.37	.58*	.59*	.46***	.01
Epinephrine	.49	.38	.27	.40	.15

[a]Due to missing data, only 14 (instead of 19) subjects were used in correlational analysis between catecholamine measures and Figley scores.
*$p < .0125$ (When Bonferroni corrections are used, only results occurring with a probability of .0125 or less are considered statistically significant); ** $p < .02$; *** $p < .05$.

with age-comparable normal males and other diagnostic groups (Kosten et al., 1987). Furthermore, the results suggest that increased urinary catecholamine output may be related to current symptom severity.

The relationship between symptom severity and catecholamine excretion could not be addressed in the previous study, largely because of the lack of longitudinal symptom improvement during the course of hospitalization. In the previous study, urine samples and clinical ratings were obtained from patients at four different phases of hospitalization. The PTSD patients showed consistently higher NE and EPI excretion at every time point sampled compared with patients with major depressive disorder, paranoid schizophrenia, and undifferentiated schizophrenia. However, the findings from that study showed that urinary NE and EPI, as well as Brief Psychiatric Rating Scale scores were unchanged during the course of hospitalization in the PTSD group. The refractory nature of chronic PTSD symptoms during hospitalization in patients who are hospitalized in a general psychiatric ward is not unusual. Thus, in order to investigate the relationship between catecholamine excretion and PTSD symptoms, we studied subjects across a wide range of symptom severity and focused subject recruitment on outpatients (who we assumed would be less symptomatic) as well as inpatients.

In the present study, PTSD inpatients were found to be significantly more symptomatic than outpatients. The greater degree of symptomatology in the inpatient group was paralleled by increased 24-hour urinary excretion of DA, NE, and EPI. In contrast, no significant differences were observed between outpatients with PTSD and normal controls. However, caution must be applied to interpreting this latter finding, given the small number of outpatients studied.

To our knowledge, this is the first study to investigate 24-hour urinary DA excretion in PTSD. The exact points of origin of urinary DA concentration are not known and merit further study. However, the concentration of this amine in the urine may reflect DA levels produced in the enterchromaffin cells of the gut, the small in-

tensely fluorescent cells in the sympathetic ganglia, or the kidney. It is also possible that DA may originate in the CNS. Because measures of urinary DA have not typically been included in psychoendocrine studies, little is known about the possible psychological correlates of this amine. Nonetheless, a significant elevation in urinary DA excretion was observed in the PTSD group. This elevation was related to overall severity of PTSD, and particularly to intrusive symptoms. These observations are consistent with results of a pilot study that found significant elevations in plasma DA in 12 Vietnam combat veterans with PTSD compared with eight men with major depressive disorder and eight healthy subjects (Hammer et al., 1990). Given the preliminary observations, further studies exploring the physiological significant and possible psychological correlates of urinary DA are warranted. Furthermore, given the trend for a significant relationship between Figley scale scores (which reflect intrusive, avoidance, and hyperarousal symptoms) and DA, it would be reasonable to further explore relationships between DA and hyperarousal symptoms in PTSD.

Urinary NE levels were found to be significantly different between inpatients and outpatients. Furthermore, urinary NE excretion was strongly correlated with severity of PTSD symptoms, particularly intrusive symptoms. This finding is consistent with the observation that tricyclic antidepressants and monoamine oxidase inhibitors are particularly effective in alleviating intrusive, but not other, symptoms of PTSD (Southwick et al., 1990b). In contrast, the 24-hour mean urinary EPI excretion was not found to correlate with scores on any of the symptom scales utilized, although the mean EPI excretion was significantly higher in PTSD inpatients compared with outpatients. The pronounced elevation in inpatients is consistent with our previously published study (Kosten et al., 1987). Thus, urinary EPI excretion may reflect acute adrenomedullary activity in response to stress associated with hospitalization, or with adjunctive symptoms that are more directly relevant to inpatient hospitalization, such as increased anger, suicidality tendencies, and impulsiveness. These traits have been associated with increased urinary EPI excretion in individuals without PTSD (Funkenstein, 1956; Nesse et al., 1984; Ostroff et al., 1982). Because most of our PTSD subjects were free of other axis I diagnoses, it is unlikely that the increased urinary EPI excretion in PTSD inpatients was specifically related to other major axis I conditions.

The three catecholamine measures did not show significant correlations with each other in either the PTSD group or the normal subjects at the adjusted alpha level. However, there was clearly a strong trend for a relationship between DA and NE. This is not surprising because both amines showed similar correlations with symptom severity. In contrast, EPI showed the weakest correlation to the other two catecholamines. A lack of correlation among catecholamine measures is consistent with the notion that peripheral hormone systems are governed by independent regulatory mechanisms (Mason et al., 1976, 1989, 1990). However, given the strong trends observed between some of the catecholamines, it is possible that the lack of significant correlations among the measures may be due to the relatively small sample size utilized.

A major limitation of the present study is that subjects were not maintained on monoamine-free diets prior to the collection of the urine samples; thus, it is possible that dietary influences contributed to the catecholamine levels observed. The potential contribution of dietary factors should be addressed in subsequent studies exploring the relationship between urinary catecholamine excretion and symptom severity.

Mason et al. (1990) have previously noted that the hormonal changes in PTSD are of a persistent and chronic nature, and have suggested that the magnitude and persistence of changes in NE might be a potentially useful diagnostic indicator. We now also provide evidence that urinary DA levels may be useful in this regard. The present data also suggest that in addition to diagnostic "trait-like" measures, amine levels may also reflect severity within the diagnostic grouping. The results provide encouragement for further exploration of the relationship between catecholamines and specific symptom clusters in PTSD.

Conclusion

Mean 24-hour urinary catecholamine excretion was high in PTSD inpatients compared with normal subjects. The DA and NE concentrations were positively correlated with degree of PTSD symptomatology as measured by the Impact of Events Scale, and, particularly, were related to intrusive symptoms. The existence of biological alterations that reflect specific PTSD symptom severity has potential implication for understanding both the pathophysiology of this disorder and its treatment. The results provide encouragement for further exploration of the relationship between catecholamines and specific symptom clusters in PTSD.

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